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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. 6487.US.01

First Inventor or Application Identifier Steven L. Krill

Title INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION

Express Mail Label No. EE835509626US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ * Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 35]
(preferred arrangement set forth below)
 - Descriptive title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 15]
4. Oath or Declaration [Total Pages 4]
 - a. ☒ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

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5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☐ 37 C.F.R. § 3.73(b) Statement of Power of Attorney (when there is an assignee)
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure Statement (IDS)/PTO-1449 [Copies of IDS Citations]
11. ☐ Preliminary Amendment
12. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
13. ☐ * Small Entity Statement(s) [Statement filed in prior application Status still proper and desired (PTO/SB/09-12)]
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Steven L. Krill, *et al.*

Application No.: (not yet assigned)

Group No.: (not yet assigned)

Filed:

Examiner: (not yet assigned)

For: INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION

Assistant Commissioner for Patents

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Date of Deposit 11/12/1999

I hereby state that the following *attached* papers

1. Utility Patent Application Transmittal (in duplicate)
2. Fee Transmittal Form PTO SB/17 (in duplicate)
3. Declaration and Power of Attorney (in duplicate)
4. Invention specification including:
 - Description of invention
 - Claims (23 in total)
 - One (1) page abstract
5. 15 pages of Drawings (Fig. 1-Fig. 15)
6. Return Receipt Postcard

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Kathleen T. Litz



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INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION**Technical Field of the Invention**

5 The instant invention relates to the fields of
pharmaceutical and organic chemistry, and provides novel
solid dispersion pharmaceutical formulations which
demonstrate an inhibition of crystallization.

10

Background of the Invention

One measure of the potential usefulness of an oral
dosage form of a pharmaceutical agent is the
15 bioavailability observed after oral administration of the
dosage form. Various factors can affect the
bioavailability of a drug when administered orally. These
factors include aqueous solubility, drug absorption
throughout the gastrointestinal tract, dosage strength, and
20 first pass effect. Aqueous solubility is one of the most
important of these factors. When a drug has poor aqueous
solubility, attempts are often made to identify salts or
other derivatives of the drug which have improved aqueous
solubility. When a salt or other derivative of the drug is

identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable solid dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

An alternative dosage form is a solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Sciences*, 60, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by

mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions.

Retroviral protease inhibiting compounds are useful for inhibiting HIV proteases *in vitro* and *in vivo*, and are
 5 useful for inhibiting HIV (human immunodeficiency virus) infections and for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability.

Examples of HIV protease inhibiting compounds include

- 10 2S,3S,5S)-5-(N-(N-(N-methyl-N-(2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-(5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);
- (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-1,6-diphenylhexane (ABT-378);
- N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);
- 20 N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]- (4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);
- 5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-
3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-
t-butylamide;

5 5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-
amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-
butylamide;

[1S-[1R-(R-),2S*]]-N¹ [3-[[[(1,1 -
dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-
hydroxy-1-(phenylmethyl)propyl]-2-[(2-
10 quinolinylcarbonyl)amino]-butanediamide;

VX-478; DMP-323; DMP-450; AG1343(nelfinavir);

BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or
combinations thereof.

While some drugs would be expected to have good
15 solubility in organic solvents, it would not necessarily
follow that oral administration of such a solution would
give good bioavailability for the drug.

Polyethylene glycol (PEG) solid dispersion
formulations are generally known to improve the dissolution
20 and bioavailability of many compounds. However, Aungst et
al. has recently demonstrated that this was unable to
improve the bioavailability of an HIV protease inhibitor
with a cyclic urea structural backbone, called DMP 323

(Aungst et al., *International Journal of Pharmaceutics*, 156, 79 (1997)).

In addition, some drugs tend to form crystals when placed in solution, which can be problematic during
5 formulation.

Polyvinylpyrrolidone (PVP) is known to inhibit crystallization of drugs (Yohioka, M. et al., *J. Pharm. Sci.*, 84, 983, 1995). However, prior to the instant invention, the incorporation of PVP into a second polymer
10 matrix, such as polyethylene glycol, has never been established.

U.S. 4,610,875 teaches a process for the preparation of a stable pharmaceutical dipyridamole composition containing PVP.

15 U.S. 4,769,236 teaches a process for the preparation of a stable pharmaceutical composition with a high dissolution rate in the gastrointestinal tract containing PVP, wherein the pharmaceutical agent is hydroflumethiazide, dipyridamole, hydrochlorothiazide,
20 cyclothiazide, cyclopenthiazide, polythiazide, methyldopa, spironolactone, quinidine, cyanidol, metronidazole, ibuprofen, naproxen, erythromycin, glaphenin, furosemide, suloctidil, nitrofurantoin, indomethacin, flavoxate,

phenobarbital, cyclandelate, ketoprofen, natridrofuryl, or triamterene.

Thus, it would be a significant contribution to the art to provide a stable solid dispersion pharmaceutical
5 formulation which demonstrates a lack of crystallization.

Approved for Release by NSA on 09-08-2013 pursuant to E.O. 13526

Summary of the Invention

The instant invention provides a stable solid dispersion pharmaceutical formulation comprising a
5 pharmaceutical compound, a water soluble carrier, such as polyethylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

Also provided by the instant invention is a
10 pharmaceutical composition comprising a stable solid dispersion as described above with additional pharmaceutically acceptable carriers, diluents, or excipients.

Additionally provided by the instant invention is a
15 method for preparing a stable solid dispersion as described above.

The instant invention still further provides methods of treatment comprising administering an effective amount of a stable solid dispersion as described above to a mammal
20 in need of such treatment.

Brief Description of the Figures

Figure 1 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated within PEG alone.

5 Figure 2 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated with a PVP/PEG matrix.

Figure 3 illustrates the DSC thermograms of PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms
10 the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 4 illustrates the DSC thermograms of PVP/PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the
15 dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 5 illustrates the effect of PEG or PVP on the crystallization rate of amorphous ritonavir. The heat of fusion was used to calculate percent crystallized. In the
20 presence of PVP the crystallization rate is slower.

Figure 6 illustrates the inhibition of crystallization using PVP.

Figure 7 illustrates PXD patterns of ABT-538 dispersions with and without PVP stored at 50°C. The data

demonstrate the improved physical stability of amorphous ABT-538 on storage.

Figure 8 illustrates PXD patterns of fenofibrate dispersions with and without PVP.

5 Figure 9 illustrates PXD patterns of fenofibrate dispersions with and without PVP and PEG.

Figure 10 illustrates PXD patterns of fenofibrate dispersions with and without PEG.

10 Figure 11 illustrates PXD patterns of fenofibrate dispersions with and without 10% PVP and PEG.

Figure 12 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 13 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

15 Figure 14 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 15 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Detailed Description of the Invention

This invention pertains to the preparation of solid dispersion systems for pharmaceuticals which demonstrate a
5 lack of crystallization.

The invention involves dispersion in a hydrophilic matrix of pharmaceuticals which exhibit poor aqueous solubility. The intent of such a formulation is to improve the aqueous dissolution properties and ultimately achieve
10 improved bioavailability. Typically, the intent of such systems is to generate a dispersion of amorphous (high energy) drug within the matrix. The presence of the high energy drug form usually improves the dissolution rate. However, these systems are not often physically stable.
15 The drug can crystallize over time, causing the loss of the desired properties and reduced shelf-life. The current invention enhances the physical stability of such formulations, thereby making this type of formulation more feasible.

20 In the instant invention, PEG 8000 is used as the hydrophilic matrix. Also employed in this formulation is polyvinylpyrrolidone (PVP), which is an example of a hydrophilic, amorphous polymer, and is used to inhibit crystallization. Other hydrophilic, amorphous polymers

include hydroxypropylmethylcellulose (HPMC), or other pharmaceutically acceptable hydrophilic, amorphous polymers. Specifically, PVP PF 17 is used within the PEG matrix to inhibit the crystallization of the drug of interest. A range of 1%-95% (w/w) of PVP can be employed, with a range of 1%-15% (w/w) being preferred.

The benefits of incorporating PVP into the PEG matrix are two fold. Firstly, processing PVP can be difficult due to its hygroscopicity. Secondly, when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug. Another benefit of adding PVP is an increase in amorphous volume of the polymer matrix where drugs may reside. Since polyethylene glycols tend to be highly crystalline, this increase in amorphous volume could be important for fast dissolution. PVP has the added advantage of having a high T_g, which imparts stabilization of amorphous regions by reducing mobility. Therefore, this invention affords the benefits of the PEG properties in a dispersion along with those of PVP.

A solid (molecular) dispersion comprising an HIV protease inhibiting compound may be prepared by dissolving or dispersing the HIV protease inhibiting compound in a sufficient amount of an organic solvent followed by

dispersion into a suitable water soluble carrier. Suitable organic solvents include pharmaceutically acceptable solvents such as methanol, ethanol, or other organic solvents in which the protease inhibitor is soluble.

5 Suitable water soluble carriers include polymers such as polyethylene glycol (PEG), pluronics, pentaerythritol, pentaerythritol tetraacetate, polyoxyethylene stearates, poly-ε-caprolactone, and the like.

The organic solvent (preferably ethanol) may then be
10 evaporated away, leaving the drug dispersed/dissolved in the molten matrix, which is then cooled. The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus improving the bioavailability of a drug exhibiting
15 dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the
20 dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the HIV protease inhibiting compound.

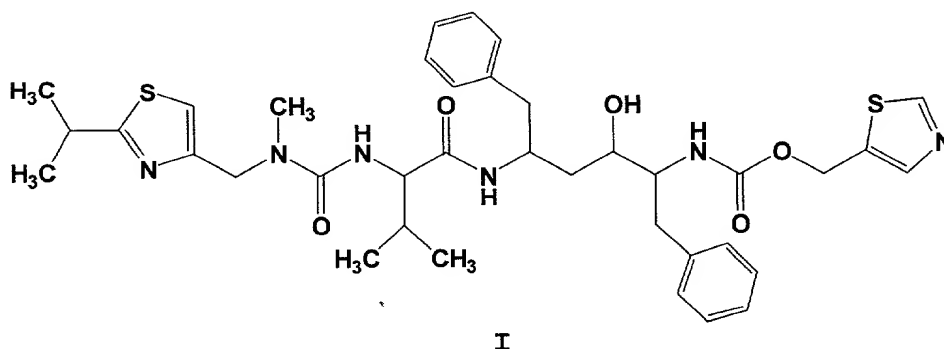
Other pharmaceutically-acceptable excipients may be
5 added to the formulation prior to forming the desired final product. Suitable excipients include lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, and the like, that might be needed to prepare a capsule
10 or tablet.

The resulting composition comprising the pharmaceutical compound may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into capsules, or made into
15 tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The composition can be used to improve the oral bioavailability and solubility of said HIV protease inhibiting compound.

20 Total daily dosing of the pharmaceutical compound may be administered to a human in single or divided doses in amounts, for example, from 0.001 to 1000 mg/kg body weight daily, but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of

submultiples thereof to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, 5 time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

One type of pharmaceutical compound that may be employed in the practice of the present invention is an HIV 10 protease inhibitor. An example of an HIV protease inhibitor is ABT-538 (ritonavir), the chemical structure of which is represented hereinbelow as a compound of formula I

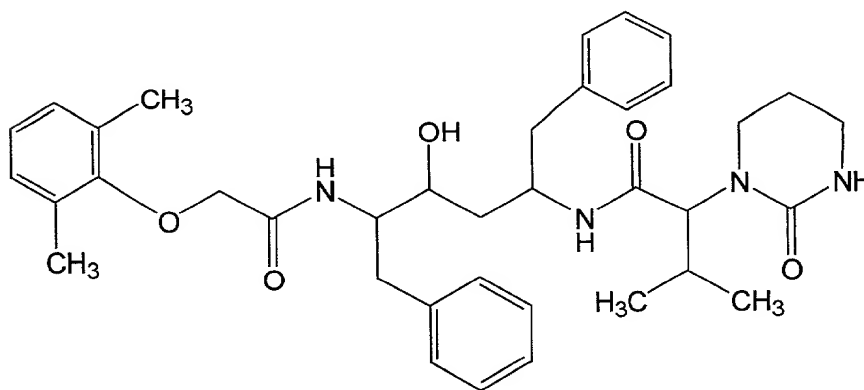


15

A compound of formula I is an HIV protease inhibitor marketed by Abbott Laboratories under the tradename Norvir[®], with the common name ritonavir [(2S,3S,5S)-5-(N-(N-(N-

methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-
L-valinyl)amino-2-(N-
((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-
hydroxyhexane]. This and other compounds as well as
5 methods for preparing same are disclosed in U.S. Patent
Nos. 5,648,497 and 5,541,206, the disclosures of which
are herein incorporated by reference.

Additional HIV protease inhibitors which may be
formulated into a solid dispersion of the instant
10 invention include compounds of formula II



II

A compound of formula II is known as ABT-378
((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-
hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-
butanoyl)amino-1,6-diphenylhexane). This and other
5 compounds, as well as methods for preparing same, are
identified in U.S. Patent No. 5,914,332, the disclosure
of which is herein incorporated by reference.

10

Other types of pharmaceutical compounds which may be
employed in the practice of the present invention include
but are not limited to antibacterial agents, antifungal
15 agents such as griseofulvin, chemotherapeutic agents,
agents for treating hyperlipidemia such as fenofibrate,
and the like.

20 The following Examples are provided to further
illustrate the present invention.

EXAMPLES**Equipment:**

5

DSC

DSC measurements were made using a Mettler DSC 30 unit. Samples (4-7mg) were sealed in standard 40 μ l aluminum crucibles with a single hole punched in the lids. An empty crucible of the same type was used as a reference.

X-ray Powder Diffraction Analysis

An X-ray powder diffraction (XPD) pattern was obtained with a Scintag[®] XDS 2000 θ/θ diffraction system equipped with a 2 kW normal focus X-ray tube and a liquid nitrogen cooled germanium solid state detector.

Isothermal Calorimetry (TAM)

The recrystallization reactions of 30% ABT-538 in PEG or PEG:PVP (95:5) solid dispersions were monitored via isothermal calorimetry (Thermometric 2277 Calorimeter) at 40 °C. Since crystallization is an exothermic process, a positive power output indicates

crystallization. The magnitude of the power output at any time is proportional to the rate of crystallization. XPD was used to confirm crystallization.

5 HPLC

The potency values of all the dispersions as well as the dissolution sample concentrations were determined via HPLC.

10 The effect of PVP on the crystallization rate of the drug in each dispersion system (drug with polymer) was investigated with the appropriate experimental technique. The results of these studies are provided in Figures 1-15.

15

Three pharmaceuticals of different properties were employed to demonstrate the general applicability of the instant invention. These compounds are identified in Table 1 below:

Table 1Model Compounds

5

Property/Compound	ABT-538	Fenofibrate	Griseofulvin
MW (g/mole)	720.96	360.84	352.77
T _m (°C)	124	79	218.13
T _g (°C)	45.8	-21.7	91

Example 1

10

Dispersion Preparations**A. Ritonavir (ABT-538) Dispersion Preparation:**

15

The samples were prepared by dissolving ABT-538 in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 75 °C. The PEG 8000 was added to the hot alcohol solution with continual swirling until the PEG

20 melted. The flask was then attached to a rotary evaporator, immersed in the water bath (75 °C) under vacuum for 15 minutes to remove the ethanol. After the majority of ethanol had evaporated, the flask was immersed in an ice

bath for 15 minutes. The contents of the flask were then vacuum dried at room temperature overnight to remove residual alcohol. The dispersion was removed from the flask, gently ground, and sized to 40-100 mesh size. The drug loads used for these dispersions were 10, 20 and 30% w/w.

B. ABT-378 Dispersion Preparation:

The solid dispersion of 30% ABT-538 in 95:5 PEG8000:PVP was prepared by dissolving the ABT-538 and PVP 17 PF in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The remainder of the process was as described above. A 30% ABT-538 dispersion in 85:15 PEG8000:PVP was also prepared similarly as were dispersions of 10 or 20% PVP 17PF in PEG 8000 without drug.

C. Fenofibrate Dispersion Preparation:

20 15% Fenofibrate in PEG 8000:

Both fenofibrate and PEG 8000 were sized to 40-100 mesh prior to mixing with a spatula on weighing paper. The mixture was then added to a 25 ml beaker and heated to 85°C in a water bath until the all the material had

melted. The molten solution was then poured onto a chilled X-ray sample holder to rapidly solidify the solution. The solid sample was immediately used to monitor the crystallization rate via X-ray powder
5 diffraction.

15% Fenofibrate in 90:10 PEG 8000:PVP:

Fenofibrate (40-100 mesh) was added to the 90:10 PEG 8000:PVP control dispersion (see above) which was also
10 sized to 40-100 mesh and mixed with spatula on a piece of weighing paper. The mixture was then processed as described above for the 15% fenofibrate dispersion in PEG 8000.

15 D. Griseofulvin Dispersion Preparation:

15% griseofulvin in PEG 8000:

Both griseofulvin and PEG 8000 were sized to 40-100
20 mesh prior to mixing on a weighing paper with a spatula. The sample was then added to an 4 ml stainless steel vessel which was sealed under a N₂ atmosphere. The vessel was then immersed into an oil bath maintained at 180°C. The sample was occasionally shaken to mix the molten
25 contents. After 5 minutes the vessel was immersed into a

liquid N₂ bath for 30 minutes. The contents of the vessel were removed, gently ground and sized to 40-100 mesh.

15% griseofulvin in 80:20 PEG 8000:PVP:

5

This dispersion was prepared in a similar manner as describe above for the 15% griseofulvin in PEG 8000 dispersion using the 80:20 PEG8000:PVP control dispersion.

10

E. Results:

ABT-538:

Figure 1 shows the X-ray powder diffraction (XPD) pattern of ABT-538, processed PEG 8000, a physical mixture of the two components and the 30% solid dispersion. A similar plot is shown in Figure 2 with PVP incorporated into the matrix. It is apparent from these figures that ABT-538 is not crystalline within either matrix. Figure 3 shows the DSC thermograms of ABT-538, PEG8000, the 30% physical mixture and the dispersion. A similar plot is seen in Figure 4 for the PEG:PVP dispersion. The endotherm associated with drug melting can clearly be discerned from the other components. Thus, it is possible to follow the kinetics of ABT-538

crystallization via DSC measurements. Crystallization kinetics were determined by heating the samples to 85°C, holding them isothermally for predetermined times followed by heating through the melting transition temperature of ABT-538. The heats of fusion were determined and ratioed against the heat of fusion of the drug melting in the physical mixture, giving the fraction crystallized. The percent crystallized as a function of isothermal (85°C) hold time is shown in Figure 5. It is clear from this experiment that the presence of PVP within the matrix suppresses the crystallization rate of ABT-538.

The crystallization rate was also followed via the heat associated with crystallization of ABT-538 using a isothermal calorimetry. The shapes and magnitudes of the crystallization peaks in Figure 6 indicate that ABT-538 crystallizes more readily in the PEG matrix as compared to the PEG:PVP matrix. This stabilizing effect of PVP is also reflected in the times required for complete crystallization (time to reach baseline) which were <10 hours for PEG and >30 hours for PEG:PVP (95:5). These data support the previous DSC results.

An additional study was performed with a dispersion containing 15% PVP. The samples were held at 50°C (above

the T_g of ABT-538) and X-ray diffraction patterns were measured over time to monitor for the appearance of crystalline ABT-538. Figure 7 shows that in the presence of PVP, crystalline ABT-538 is not present after 5 272 hours, while in PEG8000 alone crystalline drug is detected at 233 hours (and before, data not shown).

Fenofibrate:

Figure 8 shows the XPD patterns of PEG 8000, 10 fenofibrate, a 15% physical mixture and the 15% fenofibrate solid dispersion. The figure illustrates that the fenofibrate is X-ray-amorphous within the matrix. A similar plot with the XPD patterns for the 15% fenofibrate dispersion in a 90:10 PEG 8000:PVP matrix is 15 presented in Figure 9. Again, the fenofibrate is amorphous. Upon storage at 25°C, the fenofibrate begins to crystallize in the PEG 8000 matrix within 1 hour (Figure 10). Additional crystallization follows upto 12 hours, when the experiment was terminated. In the 20 presence of PVP (Figure 11), the fenofibrate does not crystallize in the timeframe of the experiment. This clearly demonstrates the inhibitory effects of PVP on crystallization within the PEG 8000 matrix.

Griseofulvin:

Similar XPD patterns for the griseofulvin dispersion in PEG 8000 and 80:20 PEG 8000:PVP matrices are shown in Figures 12 and 13, respectively. In both instances, 5 amorphous griseofulvin is isolated within the respective matrices. The XPD rate of crystallization experiments show that after one hour at 25°C, griseofulvin begins to crystallize (Figure 14). However, in the presence of PVP (Figure 15), crystallization is not observed even after 10 15 hours under the same conditions. This again demonstrates the inhibitory effects of PVP amorphous drug crystallization within a PEG matrix.

E. Conclusions:

The data presented demonstrate that PVP incorporated within a hydrophilic matrix, such as PEG 8000, inhibits crystallization of drug molecules having varying physicochemical properties. Thus, the instant invention 20 has a broad application to development of viable solid dispersion formulations where the high energy amorphous (non-crystalline) form of a drug is desired.

Example 2Stability of Dispersion in Molten PEG 8000

The stability of the dispersion of ABT-538 in PEG
5 8000 in the molten state at 70 °C was examined.
Individual approximately 5 mg quantities of the
dispersion (aged for 6 weeks at room temperature) were
placed in 4 ml glass vials. These vials, with the
exception of the initial time point, were placed in a
10 70 °C oven which was sampled at pre-determined intervals,
chilled in ice water and placed in the freezer until HPLC
analysis. After all samples were collected, they were
analyzed for ABT-538 content by HPLC. The HPLC system
consisted of a Hitachi AS 4000 autosampler, SP 8800
15 ternary pump, Applied Biosystems 783 detector, and PE
Nelson Data acquisition system. Other chromatographic
details included a Regis Little Champ 5 cm C-18 column, a
mobile phase consisting of an aqueous solution of 0.1%
trifluoroacetic acid in 10 mM aqueous tetramethyl
20 ammonium perchlorate (TMAP)/acetonitrile/methanol
(55/40/5). The flow rate was 1 ml/minute, the wavelength
of detection was 205 nm, and the injection volume was 100
μl. Standard curves of peak area of ABT-538 vs.

concentration in the range of interest were compared with experimentally obtained area counts.

5

Example 3**Protocol For Oral Bioavailability Studies**

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) are
10 fasted overnight prior to dosing, but are permitted water
ad libitum. Each dog receives a 100 µg/kg subcutaneous
dose of histamine approximately 30 minutes prior to dosing.
Each dog receives a single solid dosage form corresponding
to a 5 mg/kg dose of the drug. The dose is followed by
15 approximately 10 milliliters of water. Blood samples are
obtained from each animal prior to dosing and at 0.25, 0.5,
1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug
administration. The plasma is separated from the red cells
by centrifugation and frozen (- 30 °C) until analysis. The
20 concentrations of parent drug is determined by reverse
phase HPLC with low wavelength UV detection following
liquid-liquid extraction of the plasma samples. The parent
drug area under the curve is calculated by the trapezoidal
method over the time course of the study. The absolute
25 bioavailability of each test composition is calculated by
comparing the area under the curve after oral dosing to

that obtained from a single intravenous dose. Each capsule or capsule composition is evaluated in a group containing at least six dogs. The values reported are averages for each group of dogs.

WE CLAIM:

1. A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC).
2. The composition of Claim 1 wherein said water soluble carrier is polyethylene glycol (PEG).
3. The composition of Claim 1 wherein said pharmaceutical compound is an HIV protease inhibitor dissolved in an organic solvent.
4. The composition of Claim 3 wherein said organic solvent is ethanol.
5. The composition of Claim 3 wherein said HIV protease inhibitor is 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The composition of Claim 3 wherein said HIV
protease inhibitor is (2S, 3S, 5S)-2-(2,6-
Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-
pyrimid-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane
5 (ABT-378).

7. The composition of Claim 3 wherein said HIV
protease inhibitor is a combination of 2S,3S,5S)-5-(N-(N-
((N-methyl-N-((2-isopropyl-4-
10 thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-
thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-
hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-
Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-
pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane
15 (ABT-378).

8. The composition of Claim 2 wherein said solid
dispersion is encapsulated in a hard gelatin capsule.

20 9. The composition of Claim 2 wherein said solid
dispersion is compressed into a tablet.

10. The composition of Claim 1 further comprising an
additive or a mixture of additives independently selected

from the group consisting of pharmaceutically acceptable surfactants and antioxidants.

11. The composition of Claim 1 wherein said
5 pharmaceutical compound is fenofibrate.

12. The composition of Claim 1 wherein said
pharmaceutical compound is griseofulvin.

10 13. A method of preparing a composition of Claim 1
which comprises:

- a) dissolving a pharmaceutical compound inhibitor
into an organic solvent to form a solution;
- b) adding a water soluble carrier to said
15 solution to form a mixture;
- c) adding PVP to said mixture of step b);
- d) optionally flash evaporating said solvent;
- e) optionally drying the resulting residue
remaining after evaporation;
- 20 f) optionally grinding and sieving the solid
dispersion to obtain a resultant product.

14. The method of Claim 13 additionally comprising encapsulating the solid dispersion in a hard gelatin capsule.

5 15. The method of Claim 13 additionally comprising compressing said solid dispersion into a tablet.

10 16. The method of Claim 13 wherein said pharmaceutical compound is an HIV protease inhibitor.

15 17. The method of Claim 16 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-(N-methyl-N-(2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-(5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl]amino-1,6-diphenylhexane (ABT-378).

20

18. The method of Claim 13 wherein said solvent is ethanol.

19. The method of Claim 13 wherein said water soluble carrier is polyethylene glycol (PEG).

20. A method of treating an HIV infection comprising
5 administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is an HIV protease inhibitor.

21. The method of Claim 20 wherein said HIV protease
10 inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-
15 Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl]amino-1,6-diphenylhexane (ABT-378).

22. A method of treating hyperlipidemia comprising
20 administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is fenofibrate.

23. A method of treating a fungal infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is

5 griseofulvin.

griseofulvin

Abstract

A pharmaceutical composition is disclosed which
5 comprises a solid dispersion of a pharmaceutical compound
in a water soluble carrier, such as polyethylene glycol
(PEG), and a crystallization inhibitor, such as
polyvinylpyrrolidone or hydroxypropylmethylcellulose. The
solid dispersion may optionally be encapsulated in hard
10 gelatin capsules, compressed into a tablet, or may be
granulated with a pharmaceutically acceptable granulating
agent. Also disclosed are methods of making said solid
dispersion and methods of treatment employing said solid
dispersion.

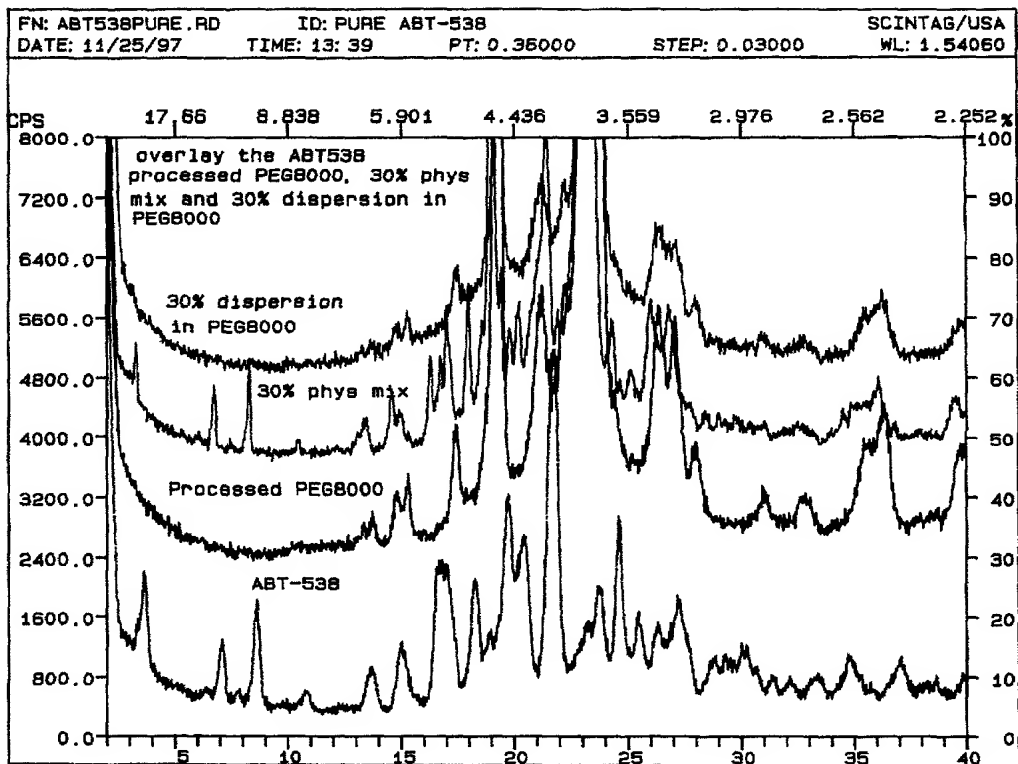


Figure 1

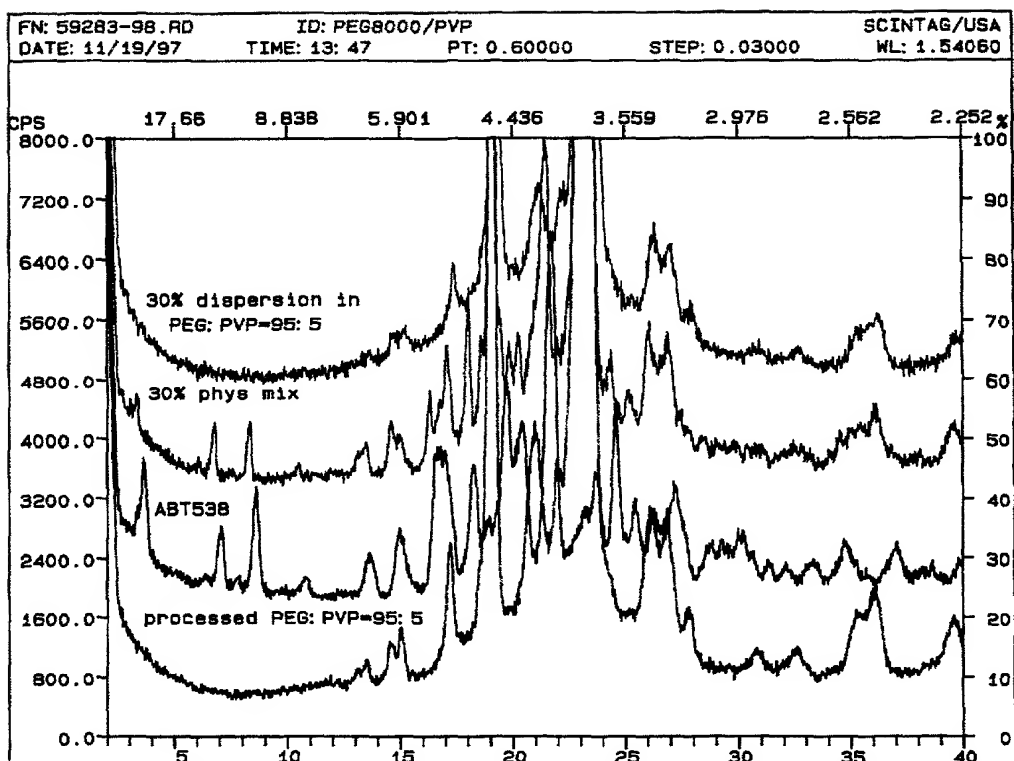


Figure 2

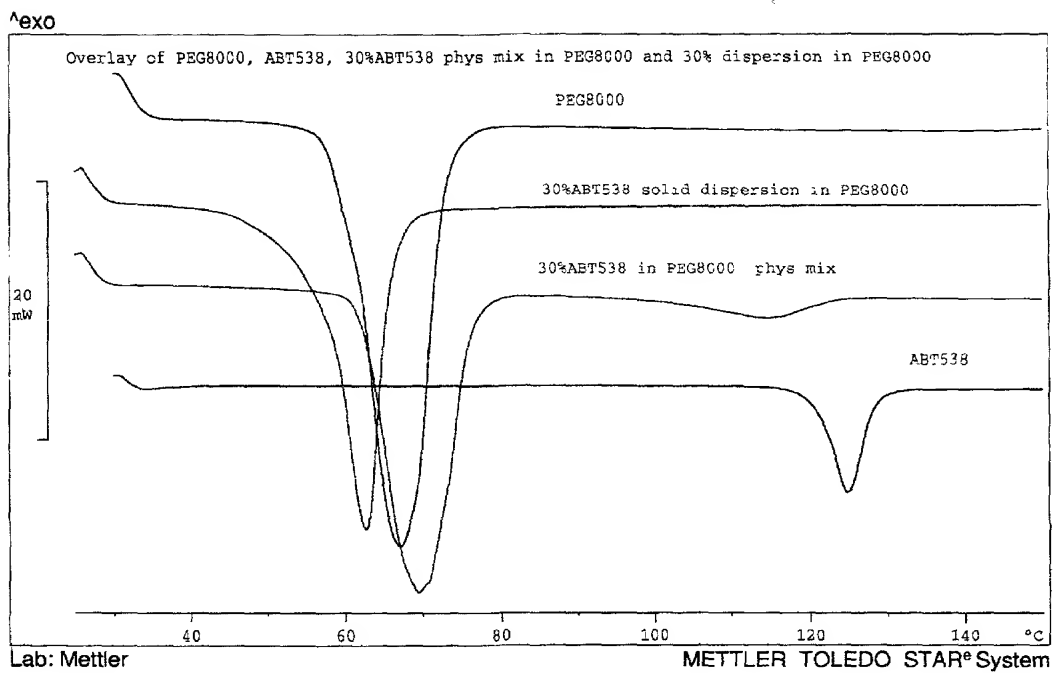


Figure 3

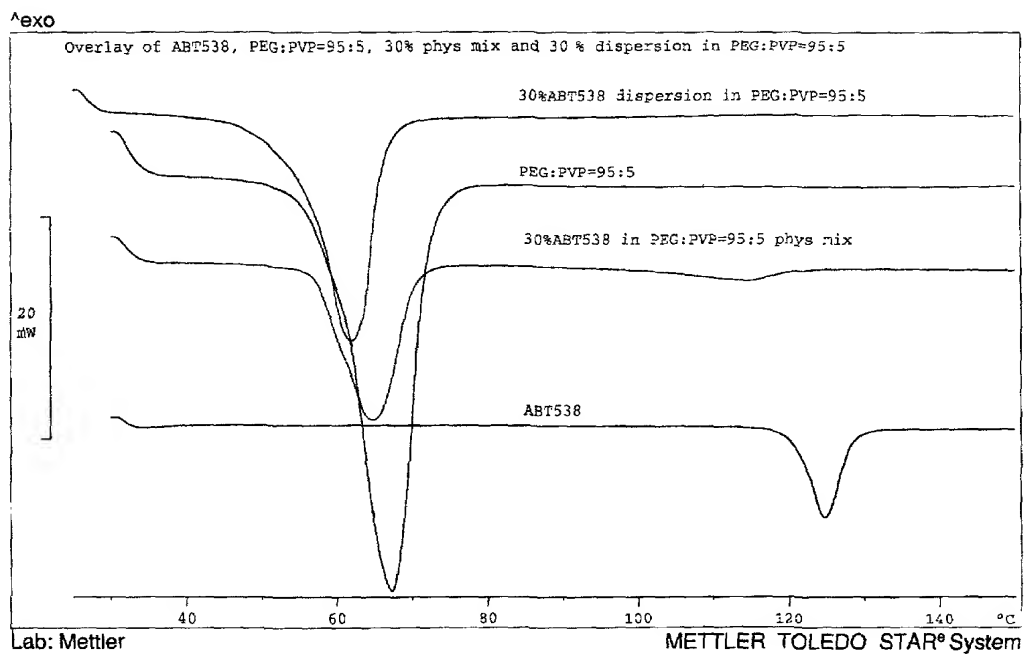


Figure 4

Crystallization of Amorphous ABT538

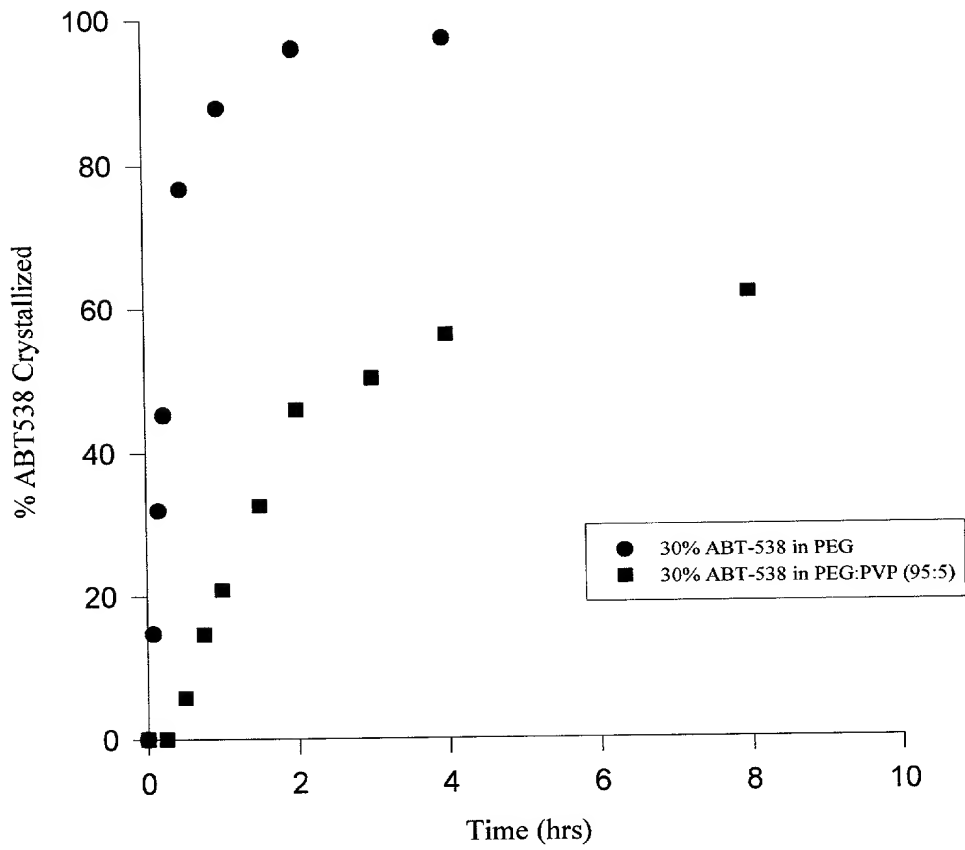


Figure 5

ABT-538 Isothermal Calorimetry (40°C)

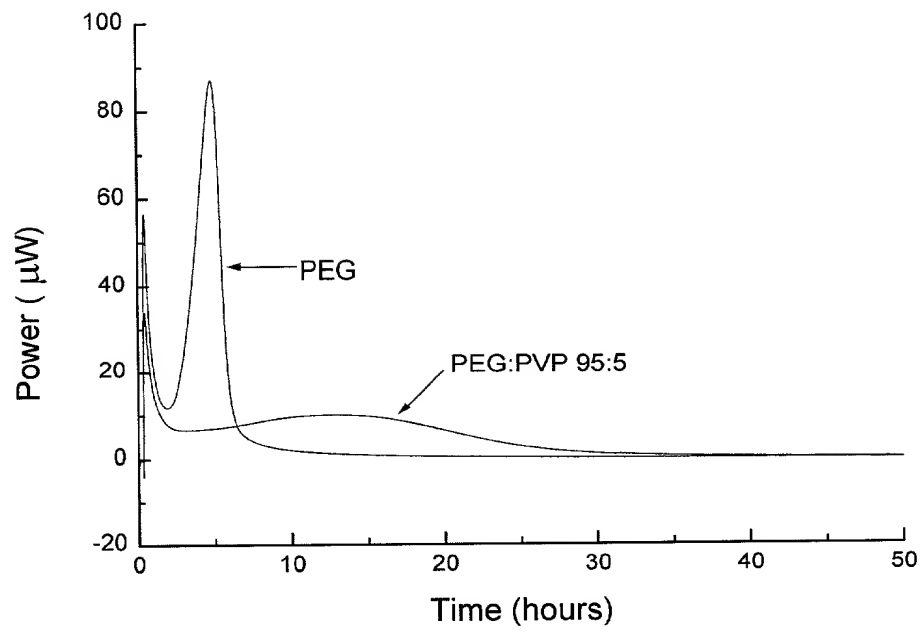


Figure 6

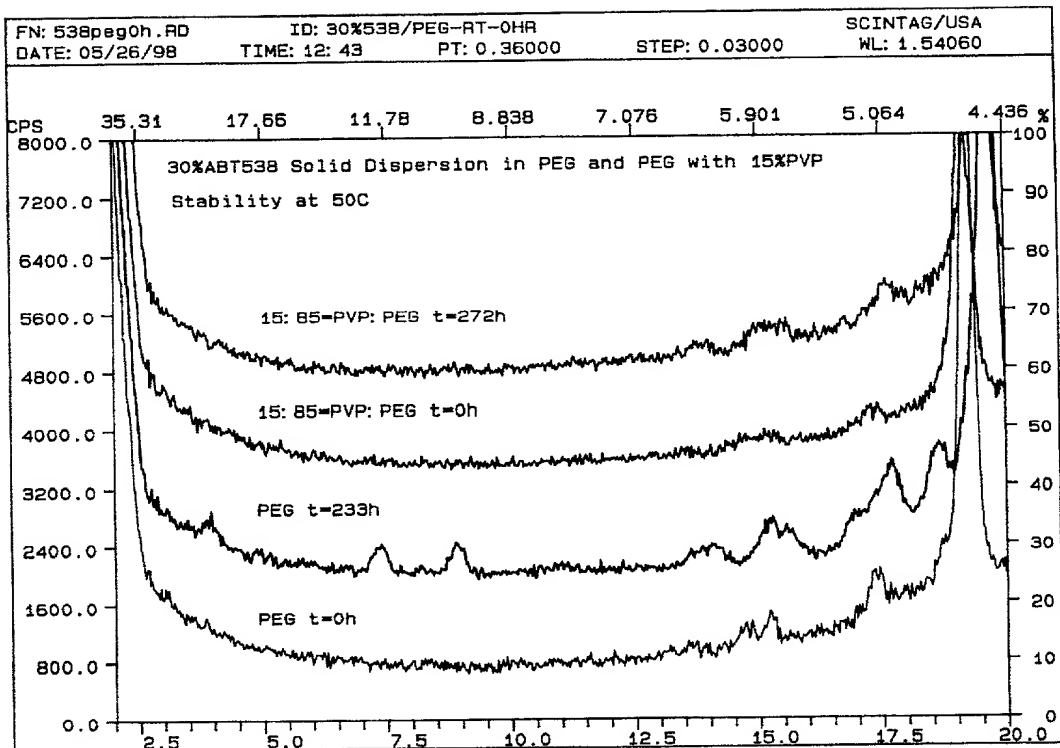


Figure 7

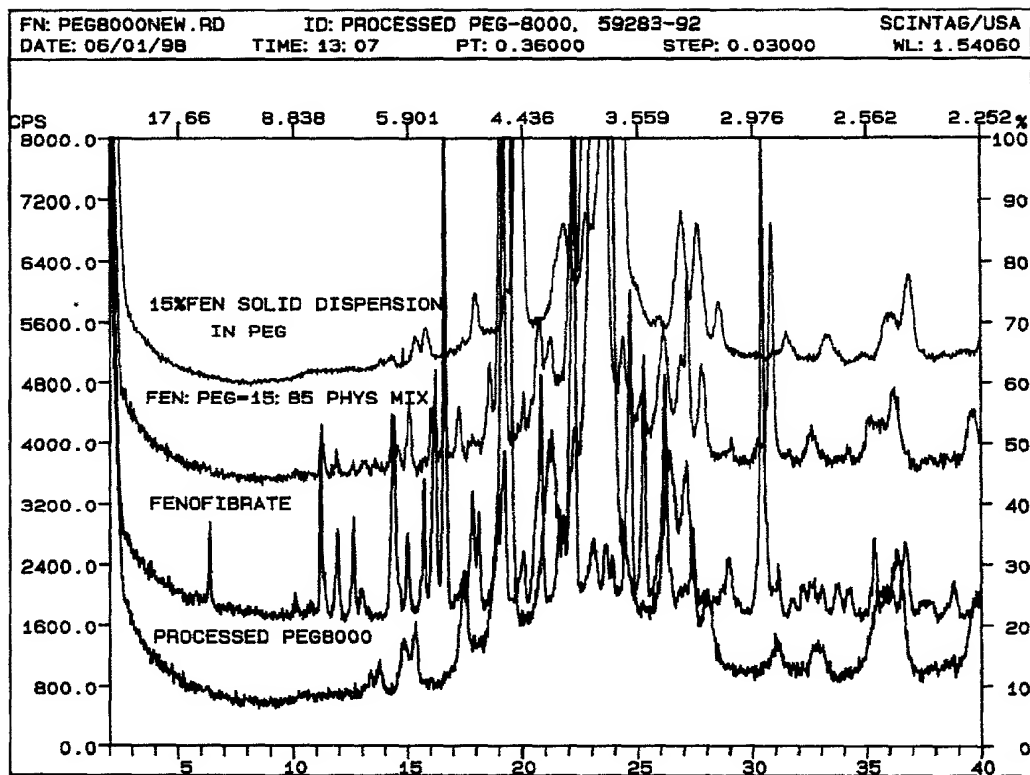


Figure 8

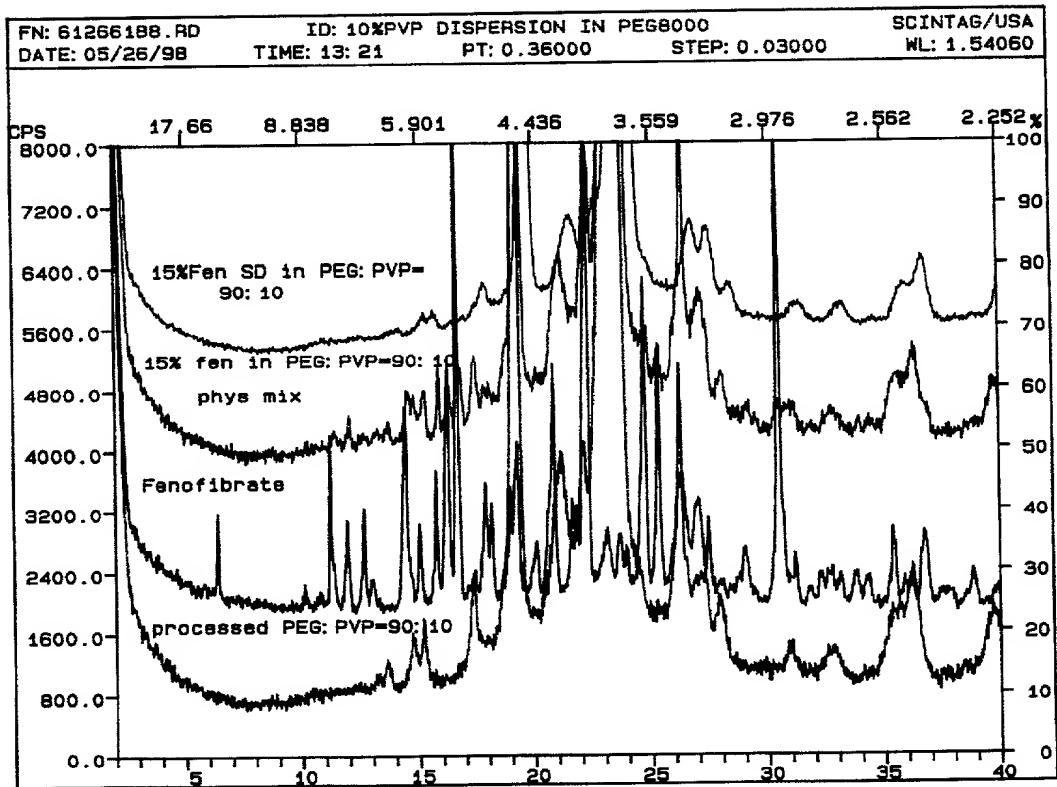


Figure 9

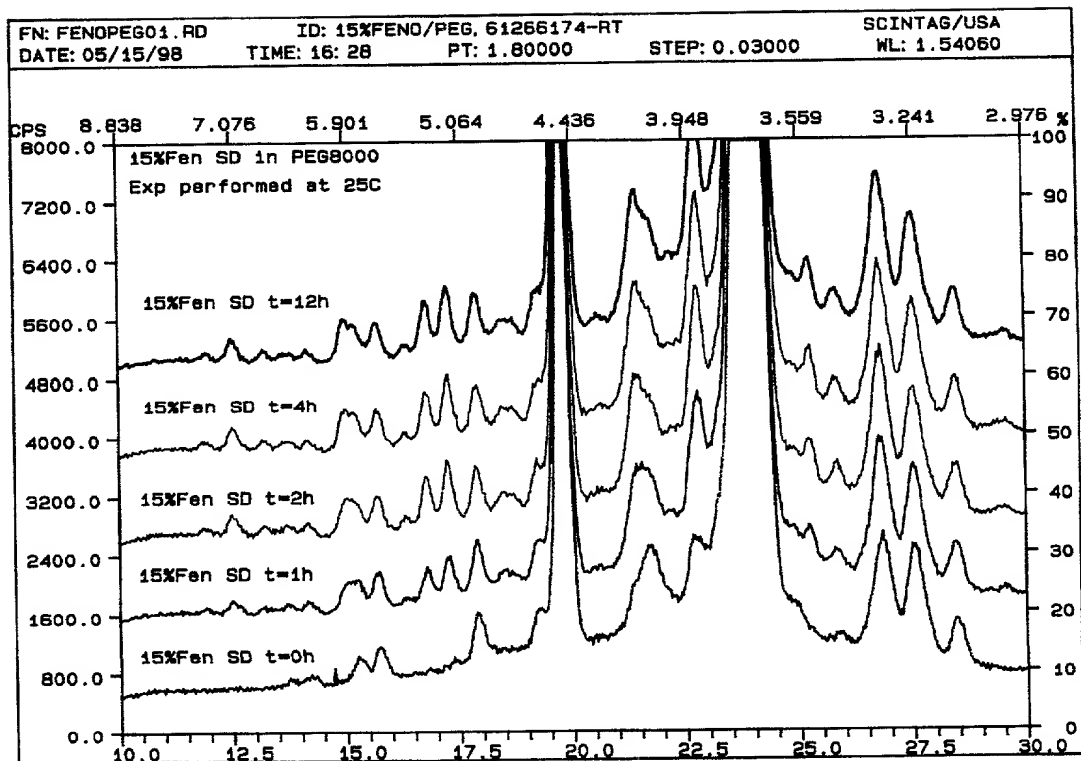


Figure 10

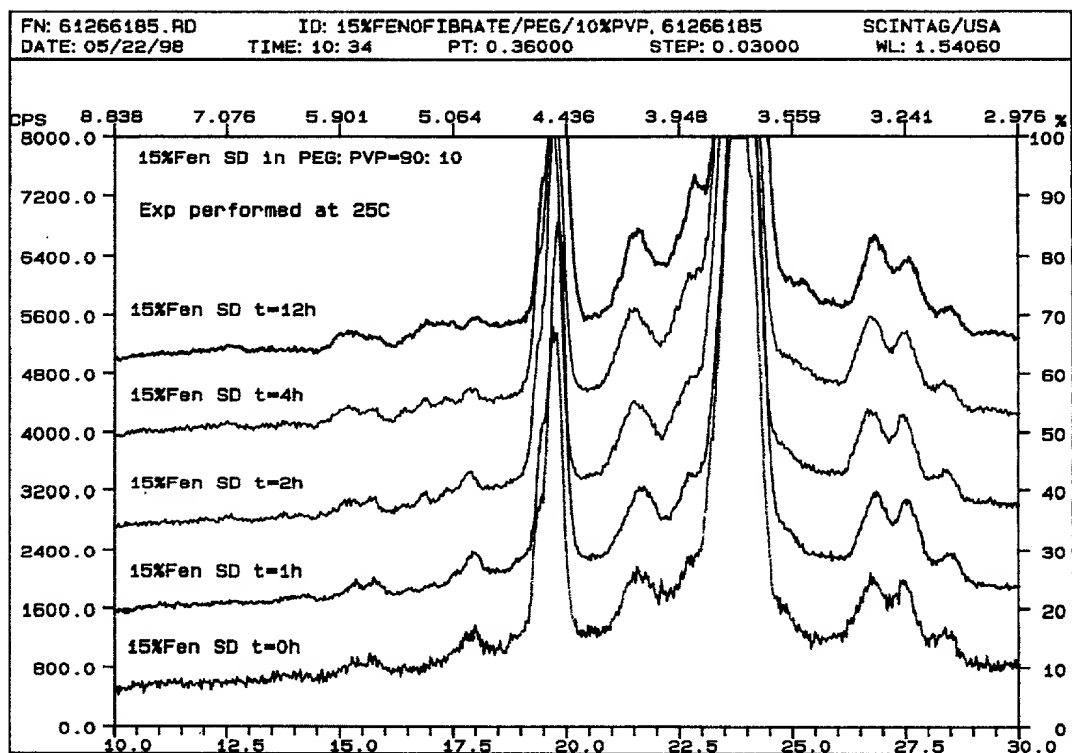


Figure 11

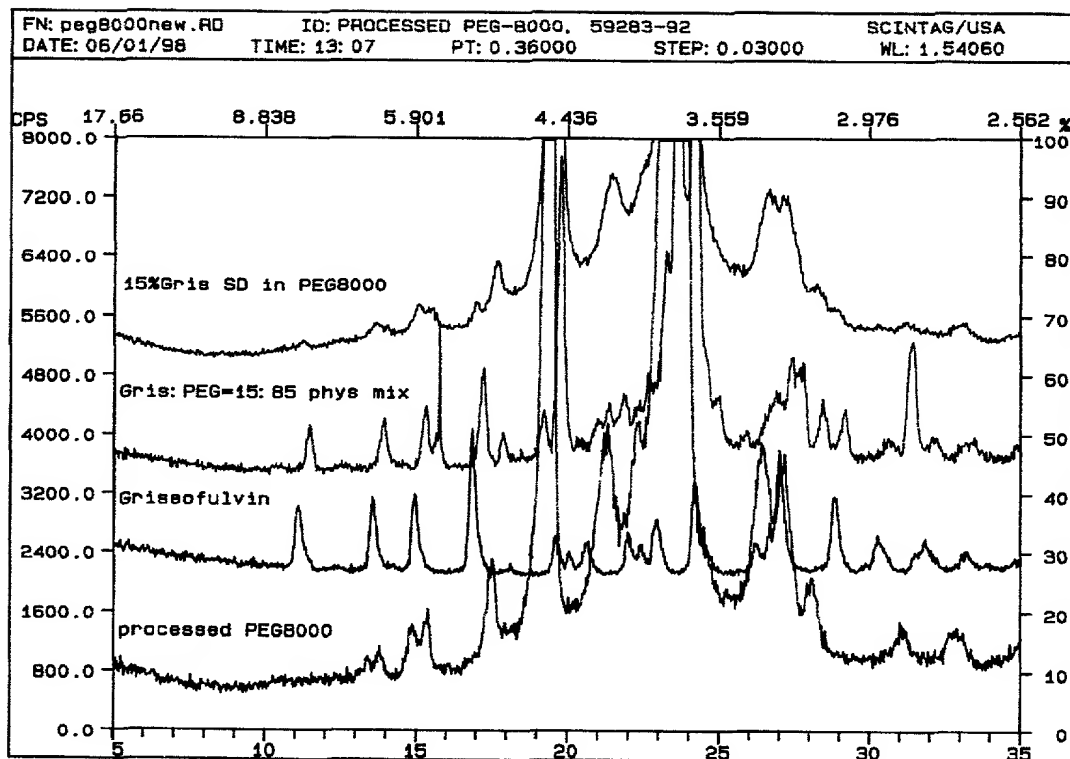


Figure 12

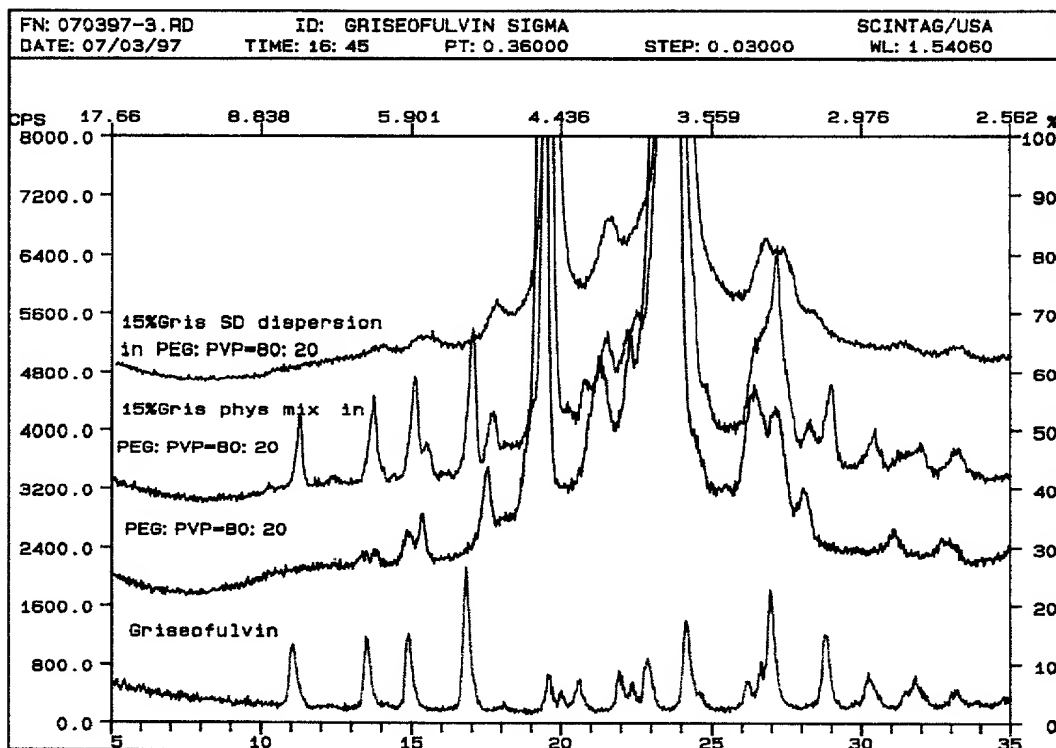


Figure 13

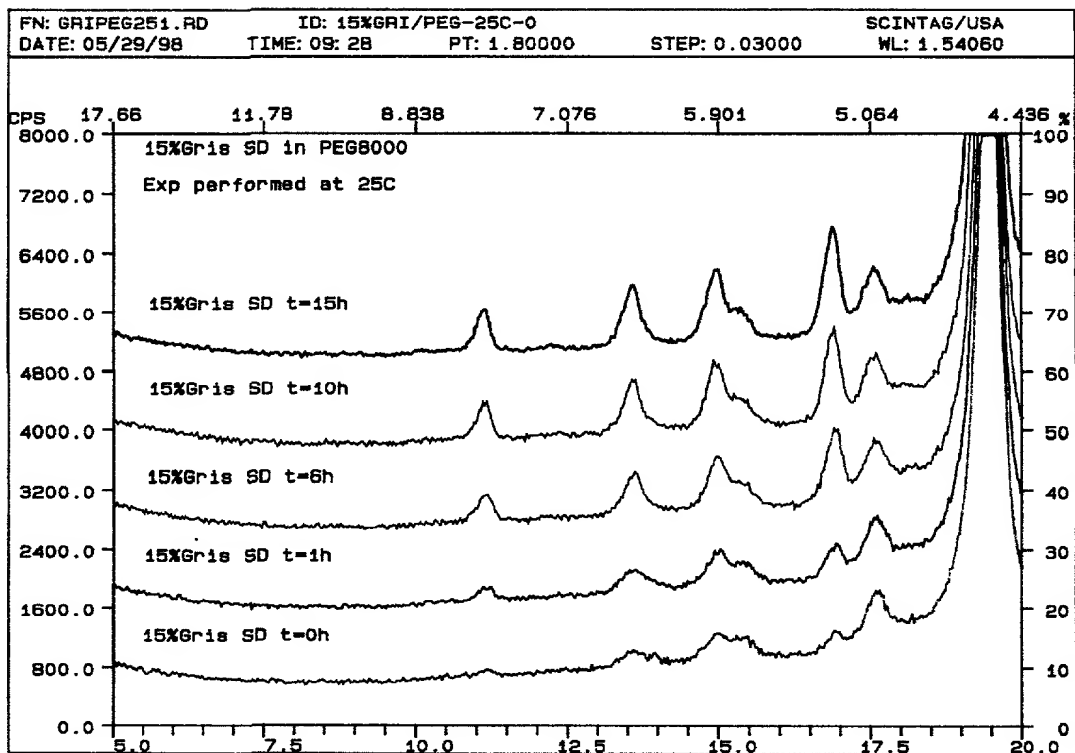


Figure 14

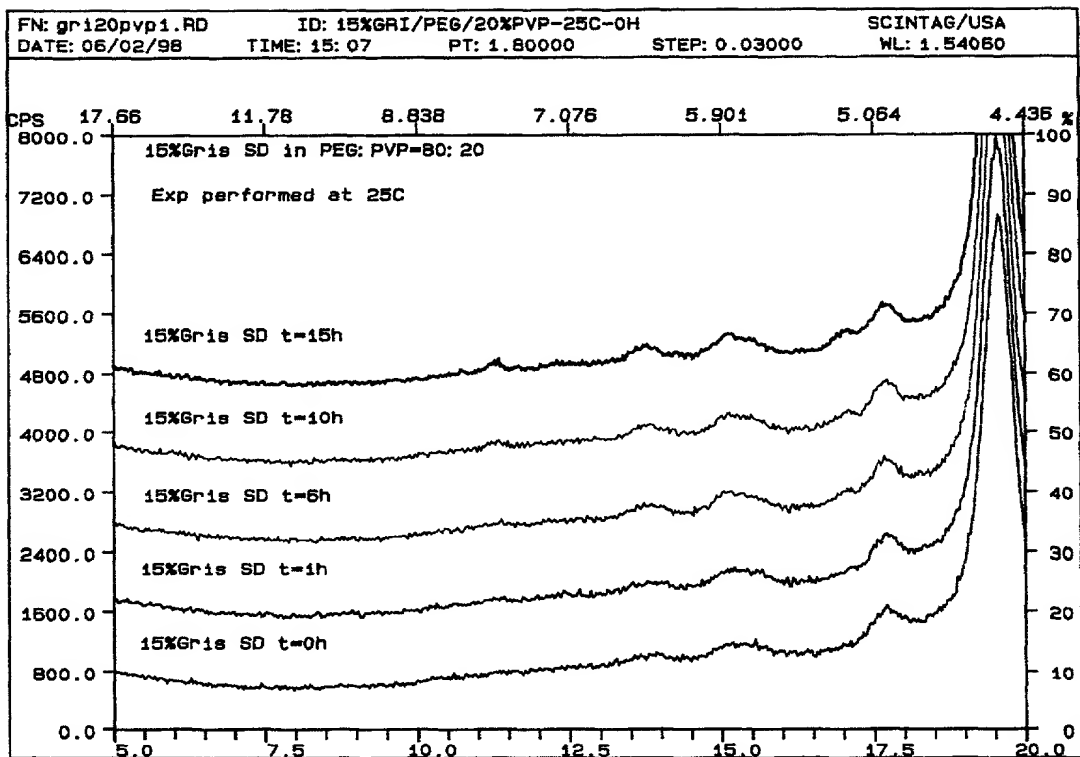


Figure 15

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Steven L. Krill, et
al.

Express Mail Label No.:
EE835509626US

Serial No.: (not yet assigned)

I hereby certify that this paper
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Title: INHIBITORS OF
CRYSTALLIZATION IN A SOLID
DISPERSION

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231, on:

Case No.: 6487.US.01

Date of Deposit: November 12, 1999

Group Art No.: (not yet assigned)

Examiner: (not yet assigned)

Kathleen T. Litz 11/12/99
Kathleen T. Litz Date

**Declaration and Power of Attorney
for a United States Patent Application**

As a below-named inventor, I hereby declare that I believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION, the specification of which is enclosed herewith.

My residence, post office address and citizenship are as stated below next to my name.

I hereby state that I have reviewed and understand the contents of the above-mentioned specification, including the claims.

I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

Claim to benefit of foreign application(s) as follows:

I hereby claim foreign priority benefits under 35 U.S.C. §119 for the following foreign applications for patent or inventor's certificate.

6487.US.01

JDS/jer

Page 1

NONE

The following foreign applications for patent or inventor's certificate have a filing date earlier than the filing date of the applications identified above.

NONE

Claim to benefit of earlier U.S. application(s) as follows:

I hereby claim the benefit under 35 U.S.C. §120 of the following earlier-filed United States patent applications. Insofar as the subject matter of each of the claims of this application is not disclosed in the prior U.S. applications in the manner required by 35 U.S.C. §112, first paragraph, I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which came into existence between the filing date(s) of the prior applications and the national or PCT filing date of this application.

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

NONE

I hereby appoint the following Attorneys and/or agents to prosecute this application and any continuation or divisional applications based hereon, and to transact all business in the Patent and Trademark Office connected therewith:

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that all statements made herein were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

James J. Fort Date

Steven L. Krill Date

Eric A. Schmitt Date

D. Law 11-12-99

Devalina Law Date

Yihong Qiu Date